UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge Oral Argument Requested

DEFENDANTS' MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' MOTION TO PRECLUDE OPINIONS OF MICHAEL B. BOTTORFF, PHARM.D.

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Pursuant to Federal Rules of Evidence 104, 403, and 702, Defendants' Executive Committee, on behalf of all Defendants in this litigation, submit this memorandum of law in opposition to Plaintiffs' Motion to Preclude Opinions of Defense Expert Michael B. Bottorff, Pharm.D. ("Motion" or "Mot.").[1]

INTRODUCTION

Defendants retained and disclosed a highly experienced pharmacokinetics and pharmacology expert, Michael B. Bottorff, Pharm.D.,[2] to analyze the metabolism of orally ingested NDMA and NDEA in order to understand exposure levels and offer a general causation opinion on whether human ingestion of these compounds at the trace amounts found in Defendants' valsartan could cause an increased risk of cancer.[3] After implementing a scientifically sound and reliable methodology, Dr. Bottorff has opined that the levels of NDMA and NDEA contained in the valsartan

[1] The expert report of Michael B. Bottorff, Pharm.D., is attached as **Exhibit A**.

[2] At deposition, Plaintiffs clearly were under the misimpression that having a Doctor of Pharmacy could only mean that Dr. Bottorff is a pharmacist who dispenses medicine from behind a drugstore counter. (*See, e.g.*, Bottorff Dep. at 48:24-49:10, 64:4-67:20, full deposition transcript attached as **Exhibit B**). This is incorrect, as Dr. Bottorff explained at length in his deposition.

[3] A drug's interaction with blood and tissue systems in the body is known as "pharmacokinetics." Essential to this analysis is the metabolism of NDMA and NDEA by specific known enzymes. The steps involved in this journey through the body are absorption, distribution, metabolism, and elimination. (Bottorff Rep. at 8, Ex. A). Pharmacology is the study of how a drug or compound works, through what mechanism(s). Pharmacodynamics is the study of what a drug or compound does to the body. (*Id.* at 19).

do not cause an increased risk of cancer in humans, whether in the liver or any other organ, because these small amounts of nitrosamines are well-below the lowest level which did *not* cause cancer in the most reliable rat studies. Dr. Bottorff has also opined that any NDMA or NDEA ingested by Plaintiffs would have been completely metabolized in the liver before reaching the bloodstream or any other downstream organs, thereby eliminating any risk of injury.

Dr. Bottorff's first-pass metabolism opinion is neither novel nor controversial. There are numerous studies published in peer-reviewed journals that hypothesize there are dose levels of NDMA which may be completely metabolized in the liver. As just one example, in the *Diaz Gomez* study,[4] cited by Dr. Bottorff and disregarded by Plaintiffs' counsel at deposition, groups of rats were given varying doses of NDMA to assess carcinogenicity. Among other findings, *Diaz Gomez* discovered that NDMA reached the kidney only after high doses were administered, leading the authors to comment, "if man and the rat are comparable, these experiments would imply that in a healthy man the metabolism and activation of [NDMA] in the diet would take place in the liver, and that the liver would remove the nitrosamine from the portal blood and prevent it reaching other organs." (*Diaz Gomez* at 499). Moreover, the World Health Organization ("WHO") also noted that

[4] Diaz Gomez, et al., The Absorption and Metabolism in Rats of Small Oral Doses of Dimethlnitrosamine, Biochem. J., 164, 497-500 (1977), is attached as **Exhibit C**.

long-term oral administration of "low doses of NDMA (<2 mg/kg body weight per day)" [5] showed a decreased incidence of kidney tumors when compared to liver, "a finding attributed to the first-pass metabolism of NDMA in the liver."[6]

In fact, Dr. Bottorff and Plaintiffs' pathology experts agree that a key step in the metabolic activation to a potential carcinogen is the hydroxylation of NDMA and NDEA through the cytochrome P450 pathways, and that the overwhelming majority of cytochrome P450 enzymes are found in the liver. (Bottorff Rep. at 26-27; Bottorff Dep. at 122:10-21, 130:2-131:2; Hecht Dep. at 293:17-294:10[7]). In other words, NDMA and NDEA have no *potential* carcinogenic effect unless and until they are metabolized by certain cytochrome P450 enzymes, which after oral ingestion, would not occur until NDMA or NDEA reaches the liver. (*See* Hecht Dep. at 292:18-21; Lagana Dep. at 327:3-6[8]; Panigrahy Dep. at 438:14-22[9]). Dr. Bottorff

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[5] As discussed below, Dr. Bottorff pinpointed a level far lower than 2mg/kg that does not cause cancer in humans.

[6] WHO, Concise International Chemical Assessment Document 38, N-Nitrosodimethylamine (2002), at 20, attached as **Exhibit D**; (citing Swenberg JA, Hoel DG, Magee PN (1991) Mechanistic and statistical insight into the large carcinogenesis bioassays on Nnitrosodiethylamine and N-nitrosodimethylamine. Cancer research, 51:6409–6414, attached as **Exhibit E**).

[7] Portions of the 8/17/21 deposition transcript of Stephen Hecht, Ph.D., is attached as **Exhibit F**.

[8] Portions of the 8/13/21 deposition transcript of Stephen Lagana, M.D., is attached as **Exhibit G**.

[9] Portions of the 9/10/21 deposition transcript of Dipak Panigrahy, M.D., is attached as **Exhibit H**.

is the *most* qualified expert[10] in this litigation to offer these opinions, which are grounded in well-established principles of pharmacokinetics. Plaintiffs' Motion clearly misses its mark and should be denied.

Plaintiffs' experts Dr. Panigrahy and Dr. Hecht also agree with Dr. Bottorff that, at certain levels, NDMA will be completely metabolized as part of first-pass metabolism and not escape the liver, and thus, not reach any downstream organs. (Panigrahy Dep. at 440:24 – 441: 4, 441:17-23; Hecht Dep. at 329:14-20). Stated another way, for NDMA to reach any other organ in the body and present any risk of cancer, it must escape first-pass metabolism in the liver. (Panigrahy Dep. at 445:9-19). These are all significant concessions by Plaintiffs' experts, which show Dr. Bottorff's opinions are reliably sound and grounded in science. Despite all of these concessions, none of Plaintiffs' experts attempted to determine the level at which these nitrosamines would escape the liver as Dr. Bottorff did, perhaps because doing so was beyond their expertise, or possibly because those calculations would undermine Plaintiffs' theory of risk just as Dr. Bottorff's opinions do here.

Moreover, Dr. Bottorff's opinion that the trace amounts of NDMA and NDEA in the valsartan do not cause an increased risk of cancer in humans is firmly rooted in a reliable methodology, which is wholly consistent with the WHO's guidance

[10] Drs. Lagana, Hecht, and Panigrahy are trained pathologists, who look at specimens under a microscope. They are not pharmacokinetic and pharmacology experts.

regarding extrapolation of animal data to humans. Contrary to Plaintiffs' unfounded assertion, Dr. Bottorff did not scale for variations in body weight when converting the non-carcinogenic doses found in rats. Instead, Dr. Bottorff extrapolated in mg/kg on a one-to-one ratio to a 70 kg human, which is widely accepted in the medical community as an average human.

Recognizing the significance of Dr. Bottorff's findings and unable to rebut his opinions with a pharmacokinetics and pharmacology expert of their own,[11] Plaintiffs now move to exclude Dr. Bottorff's opinions in their entirety through misplaced efforts to challenge his extensive education, training, and experience. But Plaintiffs have no valid basis to do so. Dr. Bottorff's qualifications are apparent and highly relevant, his methodology is both sound and accepted in his field, and his testimony and opinions fit the general causation question at issue. The Court should not exclude his opinions here.

Accordingly, Plaintiffs' Motion should be denied in its entirety.

[11] Plaintiffs have never disclosed or presented a report of a pharmacologist, pharmacist or pharmacokinetics expert who evaluated the metabolism of NDMA or NDEA, and therefore can only counter Dr. Bottorff's opinions through this misguided attempt to exclude him.

FACTUAL BACKGROUND

I. DR. BOTTORFF'S QUALIFICATIONS AND EXPERIENCE

Dr. Bottorff is a Doctor of Pharmacy with forty years' experience researching and teaching about pharmacokinetics, pharmacology, pharmacodynamics, and drug interactions. (Bottorff Rep. at 2, Ex. A). His teaching experience includes serving as Professor and Chair of the Pharmacy Practices at Manchester University, South College School of Pharmacy, and the University of Charleston. (*Id.* at 3). In his various teaching roles, Dr. Bottorff regularly instructs medical students, pharmacy students, and medical residents on how pharmaceutical drugs, including valsartan, are metabolized and pass through the body and how drugs interact with the body's systems. (*Id.* at 2). Dr. Bottorff has lectured extensively on cardiovascular topics throughout his career as well as instructing on issues related to pharmacology, metabolism, clinical benefit, and toxicities. (*Id.*). Dr. Bottorff also has thirty years of clinical experience, including rounding on hospital in-patients with cardiologists treating patients receiving drug therapy for hypertension and heart failure. (*Id.*). Dr. Bottorff has authored and continues to contribute to textbooks and journal articles, as well as give presentations, on cardiac pharmacotherapy and pharmacologic principles. (*Id.*). Dr. Bottorff has been awarded numerous research grants and has published thirty-six original research articles in peer-reviewed pharmacology journals. (*Id.*). Dr. Bottorff has also conducted several animal studies and clinical

trials on the pharmacokinetics and pharmacodynamics of drugs. (Bottorff Dep. at 72:11-23, 116:14-117:16, Ex. B).

Over the span of his forty-year career, Dr. Bottorff has reviewed the metabolic process, metabolism, distribution, toxicity, animal data, side effects, and efficacy for "*hundreds and hundreds*" of drugs and compounds. (Bottorff Dep. at 365:15-366:8) (emphasis added). Physicians, patients, and his students regularly consult Dr. Bottorff for a drug's pharmacokinetics, clinical data, and side effect profile. (*Id.* at 356:24-357:19). His methodology and analyses are the same whether the compounds are genotoxic or not. (*Id.* at 215:2-13).

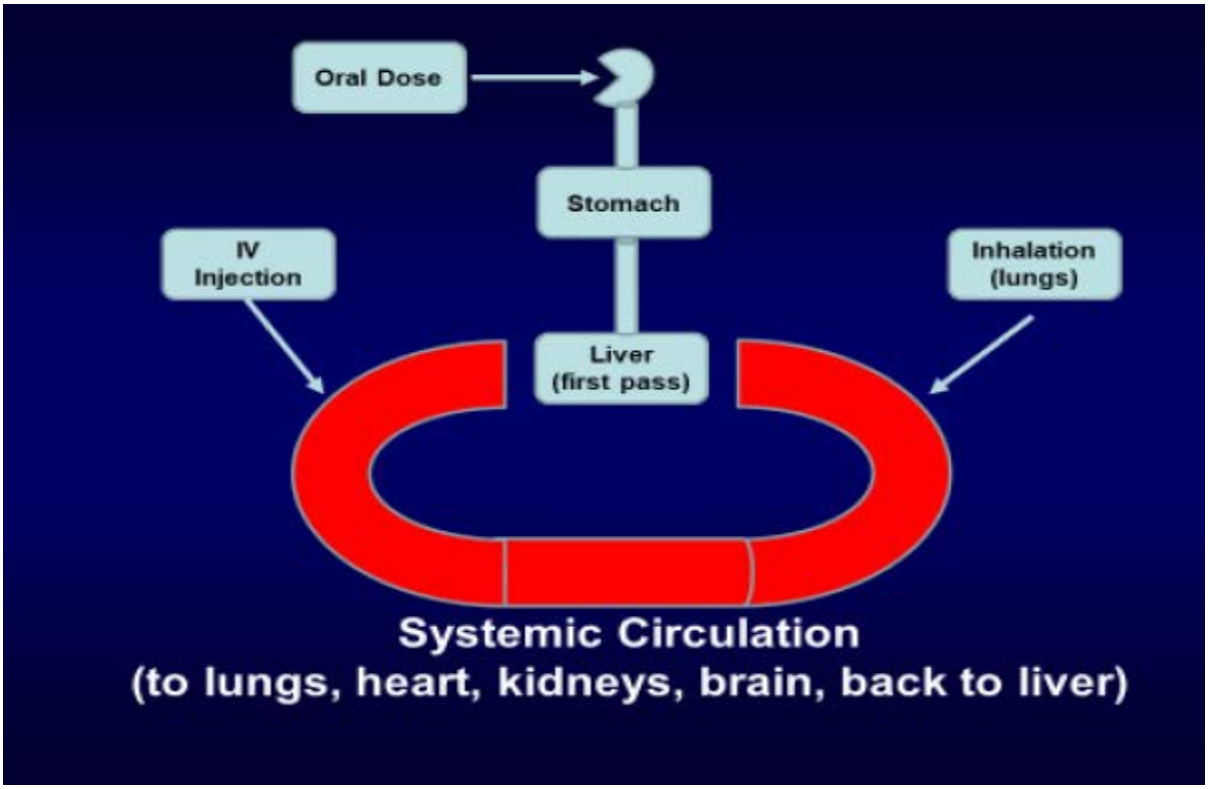
II. DR. BOTTORFF'S OPINIONS REGARDING FIRST-PASS METABOLISM AND NO INCREASED RISK OF CANCER FROM THE LEVELS OF NDMA AND NDEA IN THE VALSARTAN ARE GROUNDED IN SCIENCE.

Drawing from his unique qualifications as the only pharmacokinetics expert disclosed in this litigation, Dr. Bottorff tackled the central general causation question posed in this litigation: whether the trace amounts of NDMA and NDEA contained in the valsartan products can cause cancer in humans.

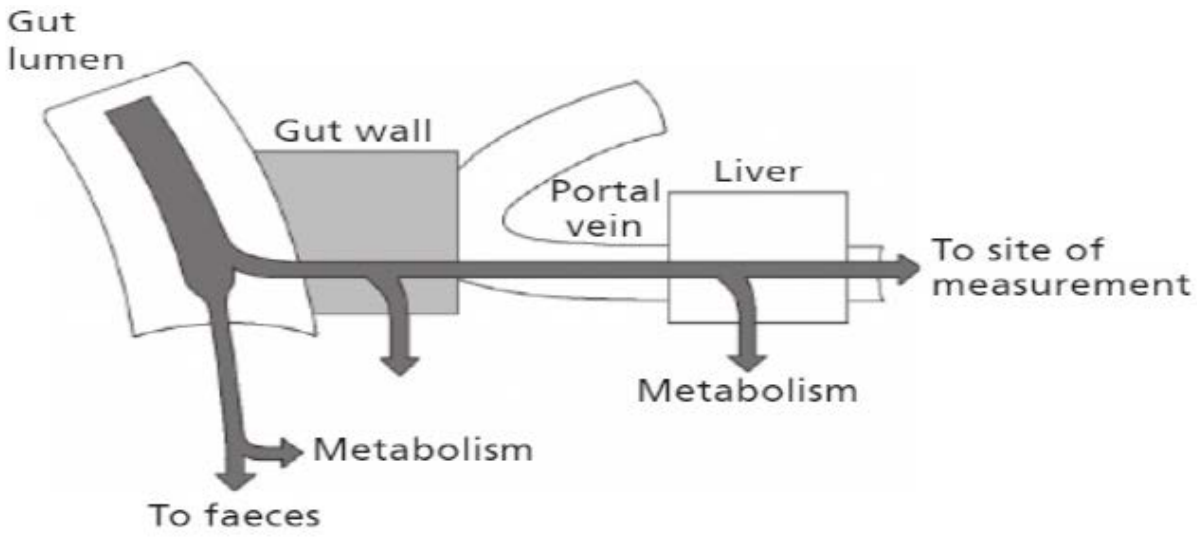
A. General Principles Of Pharmacokinetics And Pharmacology

A drug's pharmacokinetics and pharmacology are critically guided, to a large extent, by two factors: dose and route of administration. (Bottorff Rep. at 18, Ex. A). After a drug is ingested orally, it is absorbed towards the liver, across the small intestine. (Bottorff Dep. at 358:1-7, Ex. B). This metabolic step prior to a drug

reaching the systemic circulation is termed pre-systemic metabolism or *first-pass metabolism*. (*Id.* at 358:1-7). Graphically, for illustration purposes, this process is seen here:



(Bottorff Rep. at 10, Ex. A).



(Thelen K et al., Cytochrome P450-mediated metabolism in the human gut wall, J. Pharm. Pharmacol. 61:541-558 (2009), is attached as **Exhibit I**).

B. Dr. Bottorff's Review Of Medical Literature Was Comprehensive.

1. Dr. Bottorff reviewed mechanistic studies on NDMA and NDEA.

With these general principles of pharmacokinetics as background, Dr. Bottorff critically analyzed all relevant medical literature to determine how NDMA and NDEA are metabolized and distributed in the body after oral ingestion.

First, Dr. Bottorff researched the mechanistic properties, metabolic fate, and enzymatic pathways of NDMA and NDEA. (Bottorff Dep. at 130:2-131:2). To retrieve this data, Dr. Bottorff reviewed numerous publications on the well-known metabolic pathways for NDMA and NDEA.[12] The "alpha-hydroxylation" pathway produces the methyldiazonium ion, which, in turn, can mutate a well-known segment of DNA to produce the primary mutagenic and carcinogenic mutation known as the O6-methylguanine or MEG06 mutation.[13]

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[12] *See* Kushida H et al., Metabolic activation of N-alkylnitrosamines in genetically engineered salmonella typhimurium expressing CYP2E1 or CYP2A6 together with human NADPH-cytochrome P450 reductase, Carcinogenesis 21(6):1227-32 (2000), attached as **Exhibit J**; *see also* Bottorff Rep. at 27.

[13] *See* Pegg AE, Metabolism of N-nitrosodimethylamine, IARC Sci Publ. (27):3-22 (1980), attached as **Exhibit K**; *see also* Bottorff Rep. at 26-27.

As mentioned above, Dr. Bottorff opines and Plaintiffs' experts agree on the following metabolic principles of NDMA and NDEA, as outlined in the well-established body of peer-reviewed medical literature:

- A key step in the metabolic activation to a potential carcinogen is the hydroxylation of NDMA and NDEA by CYP2E1 (NDMA) and both CYP2E1 and CYP2A6 (NDEA). (*See* Bottorff Dep. at 130:2-131:2; *see also* Hecht Dep. at 293:17-20);

- The overwhelming majority of cytochrome P450 enzymes are in the liver. (Bottorff Dep. at 122:10-21; Hecht Dep. at 293:17-294:10);

- NDMA and NDEA have no *potential* carcinogenic effect unless and until they are metabolized by certain cytochrome P450 enzymes, which after oral ingestion, would not occur until NDMA or NDEA reaches the liver. (*See* Hecht Dep. at 292:18-21; *see also* Lagana Dep. at 327:3-6; Panigrahy Dep. at 438:14-22);

- There is a level of ingested NDMA that will be completely metabolized by the liver as part of "first-pass" metabolism. (Panigrahy Dep. at 441:17-23; Hecht Dep. at 329:14-20);

- If NDMA is successfully metabolized by the liver in first-pass metabolism, it does not reach other downstream organs. (Panigrahy Dep. at 440:24 – 441:4; 441:17-23); and

- For NDMA to reach any other organ in the body, it would have to escape first-pass metabolism in the liver. (Panigrahy Dep. at 445:9-19).

Based on Plaintiffs' experts' concessions alone, Dr. Bottorff should be permitted to offer these general principles of pharmacokinetics to assist the trier of fact with understanding the risk, if any, from the level of exposure in the valsartan.

Dr. Bottorff's opinion that the liver would completely metabolize the levels of NDMA and NDEA found in the valsartan and not enter systemic circulation is further supported by scientific literature which shows that the carcinogenic potential caused by the methyldiazonium mutation (if not repaired) is limited to the organ where the NDMA and NDEA are metabolized. (IARC (1986)).[14] In other words, the carcinogenic risk from these compounds, if any, is nullified because the distribution of NDMA and NDEA to downstream tissues, assuming they even have the capacity to metabolize these compounds, will be virtually none. (Bottorff Dep. at 122:22-123:22, 155:5-17, 219:4-22; Bottorff Rep. at 27-29).

2. The Rat Studies Provide The Best Comparable Data For Metabolism Of NDMA And NDEA Considering Dose Level Controls And Route Of Administration.

Dr. Bottorff then reviewed animal studies due to the obvious lack of clinical dose-response trials.[15] After considering all published animal data on NDMA and NDEA, Dr. Bottorff ultimately assigned the most weight to the long-term rat dose-

[14] Relevance of N-nitroso compounds to human cancer: exposures and mechanisms. IARC Sci Publ. 1987;(84):150-152. PMID: 3679342, is attached as **Exhibit L**.

[15] The ultimate question of whether long-term rat studies can or cannot *definitively* predict carcinogenicity in humans at certain dose levels will always be an underlying uncertainty in the absence of human data. It is telling that, despite all of the animal studies conducted on these nitrosamines, IARC has kept NDMA's and NDEA's designation the same. Notably, IARC's Group 2A designation alone, has been considered insufficient to satisfy plaintiffs' burden at the general causation phase in another MDL. *In re Roundup Prods. Liab. Litig.*, 390 F. Supp. 3d 1102, 1115 (N.D. Cal. 2018)

response bioassays. He did this for several reasons. First, it is well-accepted within the scientific community that the rat's metabolism best approximates that of a human. (*See, e.g.*, Pegg (1981)[16]). Second, the WHO characterized two specific dose-response rat bioassays, both of which Dr. Bottorff relied, as the "most suitable stud[ies] for exposure-responses analyses of the carcinogenic effects of NDMA ..." (WHO (2002), citing *Peto*[17] and *Brantom*[18]*;* Bottorff Rep. at 34-40). Third, these studies administered dose regimens at varying levels, enabling Dr. Bottorff to observe dose-response relationships. (*See Ito*,[19] *Peto*, *Brantom*; *see also* Bottorff Dep. 304:14-305:4 (explaining that the studies he assigned the most weight administered "dose regimens small enough to allow [Dr. Bottorff] to evaluate a noncancer-causing dose.")). Finally, the rat bioassays relied upon by Dr. Bottorff

[16] Pegg et al., Alkylation of Nucleic Acids and Metabolism of Small Doses of Dimethylnitrosamine in the Rat, Cancer Research 41, 3128-3132 (1981), is attached as **Exhibit M**. ("The rate of clearance of [NDMA] by the human liver should be similar to that in the rat, since it is known that human liver slices metabolize [NDMA] at about the same rate as the rat.")

[17] Peto R et al., Effects on 4080 Rats of Chronic Ingestion of Nitrosodiethylamine or N-Nitrosodimethylamine: A detailed dose response study, Cancer Research 51:6415-6451 (1991), is attached as **Exhibit N**.

[18] Brantom P.G., Dose-Response Relationships in Nitrosamine Carcinogenesis, The British Industrial Biological Research Association (BIBRA) (1983), is attached as **Exhibit O**.

[19] Ito N et al., Induction of preneoplastic and neoplastic lesions in rats treated N-nitroso compounds*, N-Nitroso Compounds: Occurrence and Biological Effects*, (41):597-601 (1982), is attached as **Exhibit P**.

involved an oral route of administration similar to how the valsartan tablets were ingested, compared to the totally inapplicable occupational studies of rubber workers where exposure was through inhalation, dermal, and combined with other chemicals. (Bottorff Rep. at 28-29, 48-49).

3. Dr. Bottorff Observed Levels Of NDMA And NDEA That Were Completely Metabolized In The Liver In Addition To Levels That Did Not Cause Cancer.

After examining the rat data in these multiple studies, Dr. Bottorff made two important observations: he noticed that there were levels of NDMA that did not escape the liver (*see Diaz Gomez*, Ex. C), and he pinpointed dose levels that did not cause cancer in certain treatment groups.

Using the non-carcinogenic doses from the rat studies,[20] Dr. Bottorff implemented a well-established conversion methodology where he extrapolated to a 70 kg human on a one-to-one ration and compared those amounts to the levels of NDMA and NDEA found in the valsartan. (*See* Bottorff Rep. at 32-33, 35-36, 38-39). After doing so, Dr. Bottorff found that the levels of NDMA and NDEA at issue here were hundreds to thousands of times lower than the dose amounts identified in *Ito*, *Peto* and *Brantom* as non-carcinogenic. Based on these results, Dr. Bottorff formed his opinion that the trace amounts of NDMA and NDEA found in the

[20] The non-carcinogenic doses were as follows: *Ito* (NDMA 0.1 mg/kg/day), *Peto* (NDMA 15 mcg/kg/day and NDEA 13.2 mcg/kg/day), and *Brantom* (8-11 mcg/kg/day))

valsartan do not cause or increase the risk of cancer in humans. Dr. Bottorff's further analysis of this data revealed that the dose levels of NDMA and NDEA contained in the valsartan would be completely metabolized and detoxified by the liver's first-pass metabolism, such that none of these compounds present any risk of cancer to any downstream organs. (*See, e.g.*, Bottorff Dep. at 362:12-363:5; Bottorff Rep. at 9, 27-29, 48).

Dr. Bottorff did not stop there. He further tested his first-pass metabolism opinion through an extensive review of other animal, dietary, and epidemiologic studies on NDMA and NDEA. (*See, e.g.*, Bottorff Rep. at 33, 41-56). None of these studies contained any compelling scientific evidence to the contrary requiring Dr. Bottorff to question his methodology or conclusions.

LEGAL STANDARD

Expert testimony should be allowed if the expert's specialized knowledge will help the trier of fact, and the testimony is based on sufficient facts or data and is the product of reliable principles and methods which the expert has reliably applied to the facts of the case. Fed. R. Evid. 702. The Supreme Court articulated the standard for judicial review of such testimony in *Daubert v. Merrell Dow Pharm., Inc*., 509 U.S. 579, 589, 592-93 (1993), finding the district judge must ensure expert testimony is both reliable and relevant and make a "preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid." "Rule

702, which governs the admissibility of expert testimony, has a liberal policy of admissibility." *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 806 (3d Cir. 1997).

Rule 702 "embodies a trilogy of restrictions on expert testimony: qualification, reliability and fit." *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003) (citation omitted).

First, "qualification requires 'that the witness possess specialized expertise,'" *Pineda v. Ford Motor Co.*, 520 F.3d 237, 244 (3d Cir. 2008) (quoting *Schneider*, 320 F.3d at 404), which can be based on "practical experience as well as academic training and credentials." *Betterbox Commc'ns Ltd. v. BB Techs., Inc.*, 300 F.3d 325, 328 (3d Cir. 2002) (quotations and citations omitted). This requirement is liberally construed by the Third Circuit, which has "eschewed imposing overly rigorous requirements of expertise and [has] been satisfied with more general qualifications." *In re Paoli R.R. Yard Pcb Litig.*, 35 F.3d 717, 774 (3d Cir. 1994). A broad range of knowledge, skills and training qualify a witness as an expert. *Id.*

Second, the Rule 702 inquiry requires the expert testimony to be reliably based upon scientific methods. *Paoli*, 35 F.3d at 742. "*Daubert* explains that the language of Rule 702 requiring the expert to testify to scientific knowledge means that the expert's opinion must be based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation;' the expert must have 'good grounds' for his or her belief." *Id.* (citing *Daubert*, 509 U.S. at 590). The

following have been articulated as factors to guide the Court's assessment of the reliability of proffered scientific expert testimony:

> (1) whether the theory or technique can be tested,
>
> (2) whether the theory or technique has been subjected to peer review,
>
> (3) whether there is a high rate of known or potential error,
>
> (4) whether there are standards controlling the technique's operation,
>
> (5) whether the theory enjoys "general acceptance,"
>
> (6) whether there is a sufficient relationship between the technique and methods which have been established to be reliable,
>
> (7) whether the expert witness' qualifications are sufficient, and
>
> (8) whether the method has been put to non-judicial uses.

Daubert, 509 U.S. at 593-94; *Paoli*, 35 F.3d at 742. The Supreme Court emphasized that the Rule 702 inquiry was "a flexible one" and emphasized that the individual factors are neither exclusive nor dispositive. *Daubert*, 509 U.S. at 594-595.

The Court's inquiry "must be solely on principles and methodology, not on the conclusions that they generate." *Daubert*, 509 U.S. at 595; *see also* Fed. R. Evid. 702 Advisory committee note to 2000 amendments ("If the expert purports to apply principles and methods to the facts of the case, it is important that this application be conducted reliably. Yet it might also be important in some cases for an expert to

educate the factfinder about general principles, without ever attempting to apply these principles to the specific facts of the case.").

The "fit" (or "helpfulness") prong requires that an expert's opinion(s) "fit the issues in the case," and be helpful to the trier of fact. *Schneider*, 320 F.3d at 404. "Rule 702's 'helpfulness' standard requires a valid scientific connection to the pertinent inquiry." *Daubert*, 509 U.S. at 591-92 (emphasis added).

ARGUMENT

I. DR. BOTTORFF IS A HIGHLY QUALIFIED AND EXPERIENCED PHARMACOKINETICS AND PHARMACOLOGY EXPERT.

Dr. Bottorff is the only pharmacokinetics and pharmacology expert designated by any party in this case. His experience analyzing the pharmacokinetic properties of drugs and compounds is highly relevant to the general causation question here because evaluation of the potential carcinogenicity of NDMA and NDEA must first start with an understanding of its metabolism.

As outlined above, Dr. Bottorff has served as Professor and Chair of the Pharmacy Practices at Manchester University, South College School of Pharmacy, and the University of Charleston. (Bottorff Rep. at 3, Ex. A). In his current teaching roles, Dr. Bottorff regularly instructs medical students, pharmacy students, and medical residents on how pharmaceutical drugs work in the body and how drugs interact with the body's systems. (*Id.* at 2). Dr. Bottorff has lectured extensively on cardiovascular topics throughout his career as well as instructing on issues related to

pharmacology, metabolism, clinical benefit, and toxicities. (*Id.*) Dr. Bottorff has conducted numerous animal studies that related to the pharmacokinetics and pharmacodynamics of drugs. (Bottorff Dep. at 116:14-117:16, Ex. B). Dr. Bottorff has also conducted several animal studies and clinical trials on the pharmacokinetics and pharmacodynamics of drugs. (*Id.* at 72:11-23, 116:14-117:16). Based on all of his qualifications and experience, Dr. Bottorff is more than qualified to testify about the pharmacokinetics of NDMA and NDEA, because Dr. Bottorff possesses "specialized knowledge" rooted in his practical experience, academic training and other credentials. *Waldorf v. Shuta*, 142 F.3d 601, 625 (3d Cir. 1998).

In their Motion, Plaintiffs ignore or misconstrue Dr. Bottorff's education, training, and experience, all of which clearly render him qualified to offer his opinions in this case. Plaintiffs fail to discuss, much less counter, the substantive pharmacokinetics and pharmacology aspects of his conclusions, and instead mischaracterize his well-founded methodology in a futile attempt to discredit him. Because Plaintiffs cannot counter Dr. Bottorff's opinion with a pharmacokinetics expert of their own, Plaintiffs merely point out that Dr. Bottorff is not a cancer researcher, epidemiologist, toxicologist (the types of experts they do have) — none of which is required for expertise in pharmacokinetic and pharmacology, nor relevant to Dr. Bottorff's opinions on metabolism. (Pls. Br. at 5). Plaintiffs also inaccurately claim Dr. Bottorff lacks an understanding of mutagenicity,

carcinogenicity, and genotoxins. (*Id.*). As discussed below, none of Plaintiffs' arguments regarding his qualifications are valid bases to exclude a pharmacokinetics expert from offering a pharmacokinetics opinion.

First, Dr. Bottorff *does* have an understanding of the mutagenicity and carcinogenicity of NDMA and NDEA. Just as every other expert has done in this litigation, Dr. Bottorff reviewed and considered these topics in published literature. Dr. Bottorff's understanding of the mechanistic properties of these compounds was described in his expert report and at deposition. (*See* Rep. at 26-27; Bottorff Dep. at 164:21-165:17). Plaintiffs' "gotcha" snippets of testimony, allegedly showing he is unqualified, are completely taken out of context and belied by Dr. Bottorff's testimony where he clearly discussed the alpha-hydroxylation pathway and the CYP2E1 mediated step to O6-methylguanine. (*See* Bottorff Dep. at 219:4-22).

Likewise, Plaintiffs' statement that "the only experience that Dr. Bottorff had with a genotoxin carcinogen was prescribing Actos" is untrue. (Pls. Br. at 5). Dr. Bottorff unequivocally testified he has not filled a prescription since 1982, and that he reviewed Actos and its carcinogenicity as well as other potentially genotoxic immunosuppressive drugs prior to this litigation. (Bottorff Dep. at 49:2-16, 315:8-18).

The fact that Dr. Bottorff is not a cancer researcher, epidemiologist, toxicologist or oncologist has no bearing on whether his opinions belong in this case,

because his methodology and opinions are primarily focused on the pharmacokinetic properties of NDMA and NDEA, including the metabolism and distribution of these compounds after ingestion of the trace amounts at issue here. Moreover, Dr. Bottorff is sufficiently qualified to interpret animal studies for dose-response relationships and opine whether there is a dose threshold below which there is no evidence of carcinogenicity—a practice and methodology he has employed for "hundreds and hundreds" of drugs and compounds throughout his entire career. (Bottorff Dep. at 365:15-366:8).

In sum, Dr. Bottorff's credentials and experience in pharmacokinetics and pharmacology sufficiently qualify him to opine on the absorption, distribution, metabolism, and elimination of a compound in the human body. His professional experience, including interpreting animal studies and dose-response relationships, more than qualifies to offer his first-pass metabolism opinion which will assist the trier of fact in this case.

Accordingly, Plaintiffs' Motion to Exclude Dr. Bottorff based on his qualifications should be denied.

II. DR. BOTTORFF'S OPINIONS FLOW FROM A SOUND, RELIABLE METHODOLOGY.

Dr. Bottorff's report and deposition testimony comprehensively explain how he employed a "sound methodology" in analyzing the general causation issue in this

case and relied on "sufficient facts and data" to arrive at his opinions. *In re TMI Litig.*, 193 F.3d at 677.

A. Dr. Bottorff's First-Pass Metabolism Opinion Has Been Tested In Rats And Subjected To Peer Review.

Dr. Bottorff's opinion that certain low doses are completely metabolized by the liver in first-pass metabolism has been tested and subjected to peer-review, and thus shows his methodology is reliable. *See Daubert*, 509 U.S. at 593-94.

There are numerous studies published in peer-reviewed journals which hypothesize that there are low dose levels of NDMA that may be completely metabolized in the liver. For example, in the *Diaz Gomez* study, groups of rats were given varying doses of NDMA to assess carcinogenicity. In that study, *Diaz Gomez* found that as the dose of NDMA administered to rats was decreased, "there was a disproportionately greater decrease in the amount of methylation of kidney DNA…" (*Diaz Gomez* at 499, Ex. C). In other words, rats with lower doses of NDMA experienced less damage to their kidneys, a downstream organ. These findings led *Diaz Gomez* to conclude, "if man and the rat are comparable, these experiments would imply that in a healthy man the metabolism and activation of [NDMA] in the diet would take place in the liver, and that the liver would remove the nitrosamine from the portal blood and prevent it reaching other organs." (*Id.*).

Moreover, after reviewing *Diaz Gomez*, as well as three other rat studies[21] showing less kidney alkylation at low doses of NDMA, *Pegg* (1980) theorized:

> The most probable explanation of these results is that NDMA given by oral administration is absorbed rapidly from the upper part of the small intestine into the portal blood supply and is then metabolized by the liver. Provided that the dose is sufficiently low, the liver metabolizes virtually all of the carcinogen in a 'first pass' clearance well known from the pharmacology of many of other drugs. The liver thus prevents the carcinogen from interacting with other organs such as the kidney.

(*Pegg* (1980) at 14-15, Ex. K).

All of these studies show that Dr. Bottorff's first-pass metabolism opinion has been and can be tested in rats, has been scientifically theorized as plausible, and has been subjected to peer-review. At a minimum, Dr. Bottorff should be allowed to "educate the factfinder about general principles" of metabolism of NDMA and NDEA. *See* Fed. R. Evid. 702 Advisory committee note to 2000 amendments.

Accordingly, Dr. Bottorff's methodology and opinions are reliable, and Plaintiffs' Motion should be denied.

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[21] Pegg, Alkylation of rat liver DNA by dimethylnitrosamine: effect of dosage on 06-methylguanine levels. J. Natl Cancer Inst., 54, 681-687 (1977), is attached as **Exhibit Q**; Pegg, A.E., Formation and subsequent repair of alkylation lesions in tissues of rodents treated with nitrosamines. Arch. Toxicol. (1979), is attached as **Exhibit R**; Pegg & Hui, Formation and subsequent removal of O6-methylguanine from DNA in rat liver and kidney after small doses of dimethylnitrosamine. Biochem. J., 173, 739-748 (1978), is attached as **Exhibit S**.

B. Dr. Bottorff's Review Of The Medical Literature Was Thorough And Unbiased.

Dr. Bottorff reviewed and considered all studies relevant to his pharmacokinetics and pharmacology opinions. *See In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 463 (E.D. Pa. 2014) ("sound scientific methodology requires that a scientist consider all of the scientific evidence when making causation determinations").

Plaintiffs erroneously assert Dr. Bottorff "only looked for studies that would support his opinion that the levels of NDMA in contaminated valsartan don't cause cancer …" (Pls. Br. at 6). This grossly mischaracterizes Dr. Bottorff's methodology and research. The general causation question is not just whether NDMA and NDEA can cause cancer in humans, [22] it is whether the trace amounts of NDMA and NDEA contained in the valsartan can cause cancer in humans. Here, Dr. Bottorff reliably extrapolated the non-carcinogenic doses in rats to humans, and in doing so, he did not ignore the higher doses demonstrating carcinogenicity in those very same studies. In other words, Plaintiffs misunderstand or overlook that the long-term rat bioassays (*Ito*, *Peto*, and *Brantom*) primarily relied upon by Dr. Bottorff *had* treatment groups who developed cancer at certain levels, and groups that *did not*

[22] Plaintiffs acknowledged through counsel that Dr. Bottorff does not agree NDMA and NDEA are human carcinogens. (Bottorff Dep. at 102:18-19).

develop cancer at certain other, lower levels. The following testimony shows how distorted and incorrect Plaintiffs' assertion is:

> Q. So in forming your opinions, you only considered data or studies that did not cause cancer, you didn't consider the ones that did cause cancer, correct?
> …
> A. Untrue, because many of these studies also caused cancer. But what I was interested in is if they had dose regimens small enough to allow me to evaluate a noncancer-causing dose and what that dose was and how it correlated to the amount of NDMA in the valsartan products.

(Bottorff Dep. at 304:14-305:4).

The main point of Dr. Bottorff's methodology was focused on determining whether there were non-carcinogenic doses, subject to first-pass metabolism, that do not produce cancer in the liver or any "downstream" organ. The following chart shows the results of one subgroup within the *Peto* study:

Table 7C *Dose-response relationships for incidental liver neoplasms in control and NDMA-treated males that were not thought to have died of any liver neoplasm, and whose livers came to autopsy without significant autolysis, cannibalism, or diaphragmatic hernia*

			No. with incidental malignant neoplasm of							No. with any incidental neoplasm of						
Treatment group	NDMA concentration (ppm)	No. of such rats	Liver cells	Bile ducts	Mesenchyme	Kupffer cells	Any part (*O*)	Expected (*E*)	Ratio (*O*/*E*)	Liver cells	Bile ducts	Mesenchyme	Kupffer cells	Any part (*O*)	Expected (*E*)	Ratio (*O*/*E*)
1	0	231	3	0	0	0	3	6.40	0.47	9	3	0	0	12	23.34	0.51
2	0.033	58	0	0	0	0	0	1.69	0.00	3	2	0	0	4	6.22	0.64
3	0.066	56	1	0	0	0	1	1.55	0.65	2	2	0	0	4	5.75	0.70
4	0.132	56	0	0	0	0	0	1.58	0.00	1	1	0	0	2	5.72	0.35
5	0.264	56	0	0	0	0	0	1.36	0.00	3	1	0	0	3	5.82	0.52
6	0.528	57	1	0	0	0	1	1.56	0.64	2	0	0	0	2	5.93	0.34
7	1.056	54	3	0	0	0	3	1.50	2.00	3	1	0	0	4	5.27	0.76
8	1.584	56	3	0	0	0	3	1.19	2.53	5	4	0	0	9	4.92	1.83
9	2.112	47	2	0	0	0	2	0.97	2.06	3	4	1	0	6	4.09	1.47
10	2.640	32	2	0	0	0	2	0.47	4.27	2	6	0	0	8	2.08	3.84
11	3.168	27	1	0	0	0	1	0.38	2.65	1	4	0	0	5	1.97	2.53
12	4.224	24	1	0	0	0	1	0.13	7.81	1	4	0	0	5	1.11	4.52
13	5.280	14	0	0	0	0	0	0.11	0.00	0	2	0	0	2	0.96	2.07
14	6.336	9	2	0	0	0	2	0.07	27.01	2	6	0	0	7	0.55	12.71
15	8.448	4	0	0	0	0	0	0.04	0.00	0	1	0	0	1	0.27	3.71
16	16.896	1	0	0	0	0	0	0.00	0.00	0	0	0	0	0	0.00	0.00
Total (all doses)		782	19	0	0	0	19	19.00	1.00	37	41	1	0	74	74.00	1.00

6427

(*Peto* at 6427, Ex. N). This chart demonstrates that, within this particular male rat subgroup, there were 16 treatment groups (first column from the left) receiving varying amounts of NDMA (second column from the left) with corresponding amounts of rats dying of liver neoplasms to the right. Based on the data in this subgroup and others, Dr. Bottorff observed an apparent increase in cancer for doses above 0.3 ppm. (Bottorff Dep. at 197:11-19). Contrary to Plaintiffs' unsupported claims, this chart shows Dr. Bottorff considered studies with doses that caused cancer. The same is also true for the *Ito* and *Brantom* studies, which similarly reported carcinogenic and non-carcinogenic outcomes in varying doses. (*See also Ito* at 598-599, *Brantom* at 62-72).

Notably, Dr. Bottorff reviewed *fourteen* other animal studies in his report and described, when available, the dose levels that did and did not produce cancer in those subjects. (*See* Bottorff Rep. at 41-49). The majority of these studies involve the rat with the exception of two mouse studies and a non-human primate study. (*Id.* at 44, 46-47). Dr. Bottorff also considered pharmacokinetic studies involving monkeys, pigs, and beagles, but ultimately discredited them due to their respective incongruent amounts of CYP2A1 compared to humans, thus making any extrapolation unreliable. (Bottorff Dep. at 178:3-22, 178:24-179:15, 274:1-7).

By considering all available literature, Dr. Bottorff has "adequately accounted for obvious alternative explanations" and his methodology was reliable. *See Miller*

v. U.S., 287 Fed. Appx. 982, 984 (3d Cir. 2008) (citation omitted). Accordingly, Dr. Bottorff did not ignore contrary evidence refuting his opinion, and Plaintiffs' Motion should be denied.

C. Dr. Bottorff Considered Mechanistic, Dietary, And Occupational Exposure Studies.

Plaintiffs claim "Dr. Bottorff failed to consider entire categories of evidence, such as mechanistic, dietary, and occupational exposure studies." This is false. His extensive review of these categories of literature is detailed below.

1. Mechanistic Studies

Contrary to Plaintiffs' assertion, Dr. Bottorff reviewed numerous studies concerning the mechanistic properties of NDMA AND NDEA, including the mechanism of action underlying its potential carcinogenicity and their well-understood metabolic processes involving the cytochrome P450 enzymes. (See Bottorff Rep. at 26-27). The following sources appear in his report:

- WHO / IARC (International Agency for Research on Cancer World Health Organization), IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Some N-Nitroso Compounds Vol. 17 (May 1978);
- EPA, Technical Fact Sheet - N-Nitroso-dimethylamine (NDMA) (2014);
- EMA, Assessment Report: Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group 15 fig. 7 (2019);
- Liteplo RG et al. (WHO), Concise International Chemical Assessment Document 38: N-nitrosodimethylamine, January 2002 IPCS Concise International Chemical Assessment Documents (2002);

- Kushida H et al., Metabolic activation of N-alkylnitrosamines in genetically engineered salmonella typhimurium expressing CYP2E1 or CYP2A6 together with human NADPH-cytochrome P450 reductase, Carcinogenesis 21(6):1227-32 (2000);

- Bellec G. et al., Cytochrome P450 Metabolic Dealkylation of Nine N-nitrosodialkylamines by Human Liver Microsomes, Carcinogenesis 17(9):2029-2034 (1996); and

- Pegg AE, Metabolism of N-nitrosodimethylamine, IARC Sci Publ. (27):3-22 (1980).

(*See* Bottorff Rep. at 26-29). And not only did Dr. Bottorff cite these in his Report, he also substantively discussed the mechanistic properties of NDMA at deposition. (Bottorff Dep. at 122:22-123:22, 155:5-17, 219:4-22). Thus, Plaintiffs' statement that Dr. Bottorff did not review mechanistic studies is misplaced and unavailing.

2. Dietary, occupational, and other studies

Likewise, Dr. Bottorff reviewed and considered all of the same dietary, occupational, and other epidemiological studies that Plaintiffs' own experts considered. Dr. Bottorff either explained in his report or at deposition[23] why those studies are unreliable. (Bottorff Rep. at 48-56, 58-62).

Dr. Bottorff considered various dietary studies, but they did not affect his first-pass metabolism opinion due to glaring deficiencies, such as lack of dose-response

[23] Plaintiffs' counsel only inquired about the dietary studies at deposition and did not cross-examine Dr. Bottorff on his criticisms of the occupational studies.

data, and potential confounding factors, such as endogenous production of nitrosamines after ingestion of food. Dr. Bottorff testified, "It is my opinion that looking at the dietary studies that have been done, I don't believe they reliably and consistently show that they have caused cancer through dietary studies." (Bottorff Dep. at 251:10-16). Consistent with his testimony, Dr. Bottorff meticulously outlined the unreliable aspects of the dietary studies in his report. (*See, e.g.,* Bottorff Rep. at 50-56) (discussing unreliability of the dietary studies due to poor controls of other cancer risk factors, unreliable FFQs or food frequency questionnaires, unspecified amounts of NDMA and duration).

Dr. Bottorff also considered the same occupational studies, including *Hidajat*, *Straif,* and *McElvenny*, as well as other epidemiological studies relied upon by Plaintiffs' experts. But these studies did not provide any reliable data for him to consider due to, among other things, an inhalation route of exposure, lack of specific data on exposure levels, and lack of controls for other cancer-causing risk factors. (*See* Bottorff Rep. at 48-62). In his report, Dr. Bottorff explained that the rubber worker studies, *Hidajat*, *Straif,* and *McElvenny*, were not relevant to his opinions, because an inhalation route of exposure would bypass the liver's first-pass metabolism and immediately enter the bloodstream—which is not how NDMA and NDEA would be metabolized after ingestion of valsartan. Further, the rubber worker studies involved various other carcinogens other than NDMA and NDEA, including

known human carcinogens, which these compounds are not. (*See* Bottorff Rep. at 48-49). Thus, Plaintiffs' statement that Dr. Bottorff did not consider dietary and occupational studies is also incorrect.

Accordingly, Plaintiffs' Motion should be denied.

D. Dr. Bottorff's Dose Conversion To A 70 kg Human Is Generally Accepted In The Scientific Community And Has Been Put To Non-Judicial Uses.

Dr. Bottorff's dose conversion to a 70 kg (154 lbs) human is generally accepted as valid in the scientific community and has repeatedly been put to non-judicial uses. *See Daubert*, 509 U.S. at 593-94; *Paoli*, 35 F.3d at 742. Conversion to a 70 kg human has been used in medical studies for decades and has been accepted by all branches of the medical and pharmacy and nursing communities as the average human weight. (Bottorff Dep. at 262:15-23, 263:22-264:10; *see, e.g.*, Mass of an Adult, Physics Fact Book, Univ. of Ark. (2003), attached as **Exhibit T**; WHO Europe Statement on Nutrition (2021), attached as **Exhibit U**). Based on this, Dr. Bottorff's conversion methodology should pass Rule 702 muster. *Daubert*, 509 U.S. at 593-94; *Paoli*, 35 F.3d at 742.

But Dr. Bottorff also testified that even after applying his calculations to a 50 kg human instead of a 70 kg human, his conclusions would not change, because 5,000 milligrams still exceed the dose threshold identified in his first-pass metabolism opinion. Stated another way, a 50 kg human, like a 70 kg human, also

would not develop cancer from the trace amounts of NDMA and NDEA found in the valsartan.

Accordingly, Plaintiffs' Motion should be denied on this ground.

E. Dr. Bottorff Has A More Than Sufficient Knowledge Basis To Offer His Opinions In This Case.

Plaintiffs' veiled reliability attack designated as an alleged "insufficient knowledge basis" should be rejected. Plaintiffs seek to exclude Dr. Bottorff on the grounds that he never identified the bioavailability of NDMA, did not know the rate of metabolism of NDMA, and did not review studies contained within *Pegg* (1980) that show "NDMA and NDEA levels increase in the blood of humans after eating a meal." (Pls. Br. At 8). All of these statements are either factually incorrect or misunderstand those concepts and their application to Dr. Bottorff's methodology.

Plaintiffs' statement that Dr. Bottorff never identified the bioavailability of NDMA is vague, misleading, and wholly misplaced. Bioavailability is the assessment of what percent of a drug reaches systemic circulation in the bloodstream. (Bottorff Dep. at 148:21-149:2). A critical part of Dr. Bottorff's analysis was to explore whether there was a dose which would be completely captured and metabolized by the liver prior to systemic circulation and *prior* to one's ability to measure bioavailability. Although entirely irrelevant to his methodology, Dr. Bottorff explained his understanding of the bioavailability of NDMA as reported in certain rat, monkey, pig, and beagle studies, but again, those findings were entirely

dependent on the actual dose administered, which, in some of those studies, was thousands of times higher than the trace amounts of NDMA and NDEA found in the valsartan. (Bottorff Dep. at 177:13-179:15).

Plaintiffs both misrepresent that Dr. Bottorff does not know the rate of metabolism of NDMA and fail to explain how it is even important to his methodology. At deposition, Dr. Bottorff testified that he could not *recall* the exact rate of metabolism of NDMA "off the top of [his] head." (Bottorff Dep. at 190:2-5). But this does not that mean that he does not *understand* it. Dr. Bottorff explained in his report and at the deposition that NDMA has a high clearance rate, which is faster than the valsartan. (*Id.* at 189:17-24, 190:2-191:10; Bottorff Rep. at 27).

Plaintiffs also argue that because Dr. Bottorff did not read two articles[24] in *Pegg* (1980), which purportedly showed "NDMA and NDEA levels increase in the blood of humans after one meal," he ignored contrary evidence. (Pls. Br. at 8). But a simple review of these articles, *Fine*[25] and *Lakritz*,[26] reveal that these studies are completely inapposite to Dr. Bottorff's methodology and opinions.

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[24] Plaintiffs do not cite the specific references in *Pegg* in their Brief.

[25] Fine, D.R., Ross, R., Rounbehler, D.P., Silvergleid, A. & Song, L. (1977) Formation in vivo of volatile N-nitrosamines in man after ingestion of cooked bacon and spinach. Nature, 265, 753-755, is attached as **Exhibit V**.

[26] Lakritz, L., Simenhoff, M.L., Dunn, S.R. & Fiddler, W. (1979) N-Nitrosodimethylamine in human blood, Fd Cosmet, Toxicol. Vol. 18, 77-79, is attached as **Exhibit W**.

For example, *Fine* examined *in vivo* nitrosation of NDMA after ingestion of bacon, beer, and a spinach and tomato sandwich, otherwise known as the human body's endogenous production of NDMA after certain foods are ingested. (*Fine* at 753, Ex. V). Here, endogenous production of NDMA does not affect Dr. Bottorff's methodology or opinions, and further, Plaintiffs unsurprisingly failed to ask any follow-up questions after Dr. Bottorff raised this concept at his deposition:

> Q. Well, regardless of the dose, if it was found in the blood, that means it got past the liver, right?
>
> …
>
> A. Not necessarily. It could have gotten there from another source.
>
> Q. Such as?
>
> A. There's known endogenous production of NDMA. So that's possible. It could have been an environmental exposure that led to NDMA that you found.

(Bottorff Dep. at 153:5-18). In sum, Plaintiffs' failure to confront Dr. Bottorff with *Fine* at deposition or even ask a few follow-up questions on endogenous production of NDMA shows *Fine* is wholly irrelevant to Dr. Bottorff's opinions.

Likewise, *Lakritz* concerned thirty-eight subjects who had blood samples extracted and assayed for volatile nitrosamines. (*Lakritz* at 77, Ex. W). Of the thirty-eight subjects, thirty-seven were found to contain NDMA. (*Id.* at 78). *Lakritz* speculated that the NDMA may have originated "from ingestion of food containing preformed nitrosamines, from inhalation or from *in vivo* formation." (*Id.*). *Lakritz*

concluded, "[t]he relationship of the findings reported in this study to the pathogenesis of cancer in man requires further investigation." (*Id.*). Thus, *Lakritz*, like *Fine*, is irrelevant to Dr. Bottorff's methodology and opinions.

Based on the foregoing reasons, Dr. Bottorff clearly does not have an "insufficient knowledge basis" upon which to offer his opinions, and Plaintiffs' Motion should be denied.

F. Dr. Bottorff's Rat To Human Extrapolation Is Not Inconsistent With The WHO's 2002 Recommendation.

Plaintiffs' challenge to Dr. Bottorff's extrapolation from rats to humans is apparently based on a misunderstanding, because the WHO's recommendation cited in their Motion does not address his methodology. (*See* WHO (2002) at 23, Ex. D; Pls. Br. at 6-7). In addition to misinterpreting Dr. Bottorff's extrapolation method, Plaintiffs also fail to point out what alternative extrapolation calculation should have been performed. (*Id.*).

Here, Dr. Bottorff *did not* scale for variations in body surface area, which is the methodology that the WHO recommends against. Without reference to scaling for body-surface area, Dr. Bottorff's extrapolation from mg/kg on a one-to-one basis from rats to humans was proper and is a standard approach for comparing doses given to animals. Plaintiffs' misunderstanding is not a ground for exclusion.

G. Dr. Bottorff's First-Pass Metabolism Opinion Is Reliably Based On Consistent Data Across Numerous Animal Studies And Does Not Rely On "Underpowered" Studies.

Plaintiffs' primary contention here is that Dr. Bottorff's first-pass metabolism opinion "relies solely on underpowered[27] studies," but this argument also fails for several reasons. First, *Ito*, *Peto*, and *Brantom*, are just three out of seventeen total articles cited in his report, the majority of which, Plaintiffs failed to ask any questions about at deposition. Second, *Peto* is one of the largest and most robust long-term cancer bioassays ever conducted. In *Peto*, four thousand eighty inbred rats were maintained from weaning on various different concentrations of NDMA and NDEA. (Peto at 6415, Ex. N). The principal aims were to characterize the respective dose-response and dose-time relationships for the effects of these agents on different types of cancer. (*Id.*). Plaintiffs' *ipse dixit* characterization of it as "underpowered" would render every single animal study, including those which Plaintiffs' own experts rely, as "underpowered."

Further, Plaintiffs' argument that Dr. Bottorff should be excluded because he disagrees with one of *Peto's* suppositions is not a ground for exclusion under Rule 702. *See Daubert*, 509 U.S. at 595 (the court's focus "must be solely on principles

[27] As a threshold matter, Plaintiffs fail to identify what aspects of *Peto's* and *Ito's* study designs are "underpowered." For purposes of this Opposition, Defendants assume they refer to an underpowered study as one in which insufficient individuals or subjects were enrolled (or data points obtained) to draw a meaningful conclusion.

and methodology, not on the conclusions that they generate"). *Peto's* statement that the "linear relationship may remain approximately true" at small doses is far from a definitive conclusion that there is no dose threshold. (*Peto* at 6446). But even if it were *Peto's* conclusion, Dr. Bottorff can disagree with it, and Plaintiffs are free to cross examine Dr. Bottorff on this point at trial. *See, e.g.*, *Stecyk v. Bell Helicopter Textron, Inc.*, 295 F.3d 408, 414-15 (3d Cir. 2002) ("A party confronted with an adverse expert witness who has sufficient, though perhaps not overwhelming, facts and assumptions as the basis for his opinion can highlight those weaknesses through effective cross-examination."). Notably, other scientists have also questioned Peto's point about the linear relationship at small doses. *See, e.g.*, *Elder*[28] at 3 ("it cannot be decided whether the dose-response at the lower end is in fact linear or not").

In sum, Plaintiffs may disagree with Dr. Bottorff's interpretations of these studies and their usefulness, but such "issues go to the weight of the experts' testimony, and not their reliability." *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig.*, 509 F. Supp. 3d 116, 167 (D.N.J. 2020) (denying motion to exclude expert opinion as unreliable where expert determined case-control studies were entitled to greater weight than the cohort

[28] Elder. Tolerablity of risk: A commentary on the nitrosamine contamination issue, J. Pharm. Sci. 000 (2021) 1-18 (discussing study which interpreted *Peto* data), is attached as **Exhibit X**.

studies, particularly since the experts' explanations of their methods were supported by scientific reasons.).

CONCLUSION

Based on the foregoing, Dr. Bottorff is more than qualified to testify in this case, implemented a reliable methodology grounded in fundamental principles of pharmacokinetics and pharmacology, and his ultimate opinions are helpful to the trier of fact. Accordingly, Defendants respectfully request that the Court deny Plaintiffs' Motion in its entirety.

Dated: December 1, 2021

Respectfully Submitted by the Defense Executive Committee on behalf of all Defendants,

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on December 1, 2021, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ Seth A. Goldberg
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